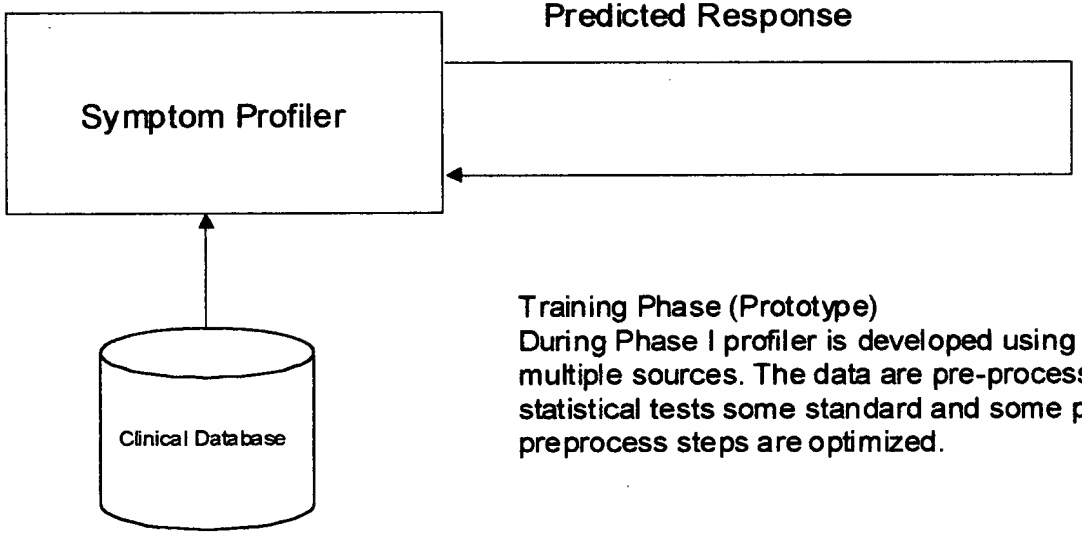
Figure 1a

Symptom Profiler Development
(Phase I)



Training Phase (Prototype)
During Phase I profiler is developed using clinical data from multiple sources. The data are pre-processed and undergo statistical tests some standard and some proprietary until the preprocess steps are optimized.

Completion Criteria:
Validation of symptom profiler is complete when system optimized

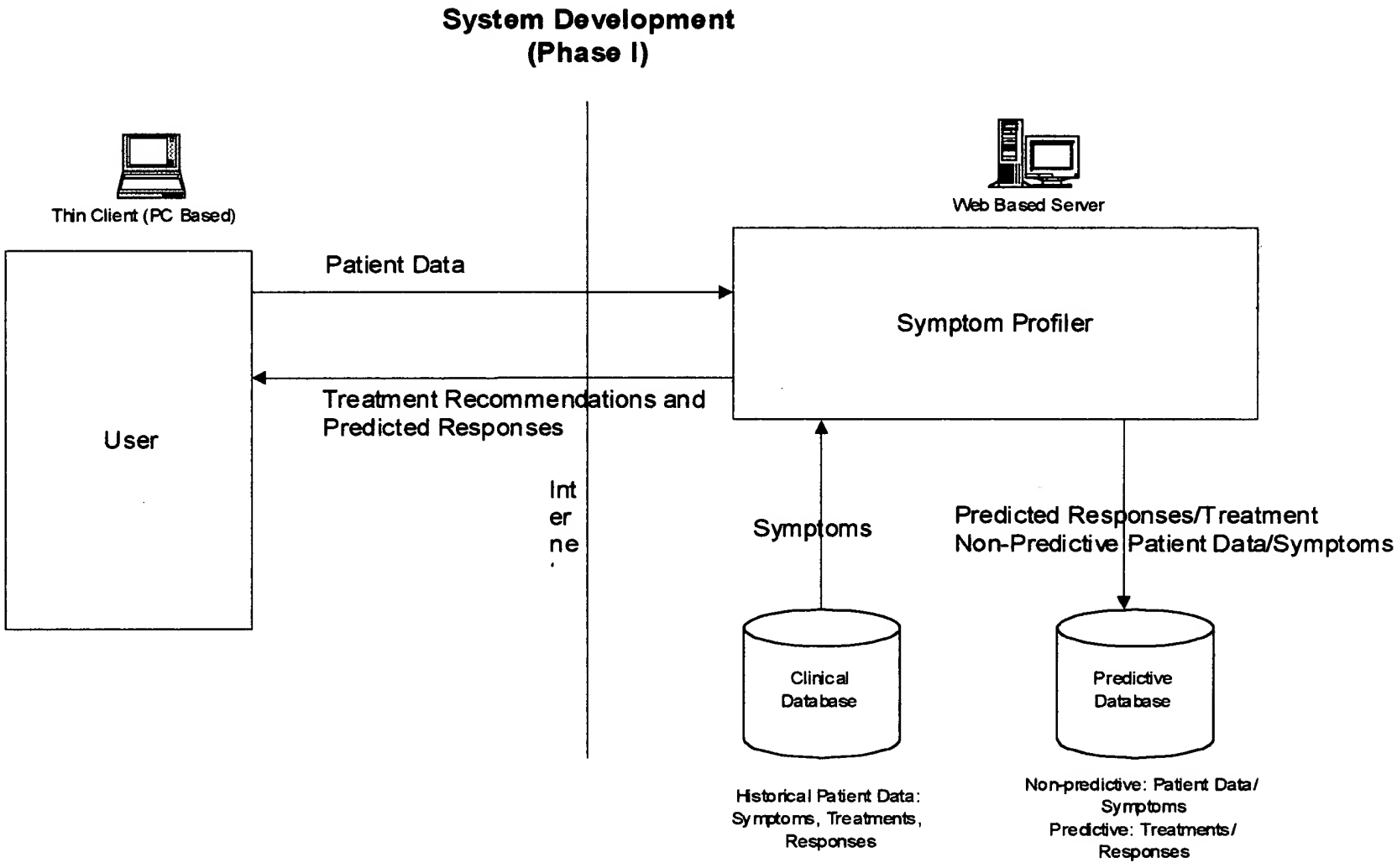


Figure 16

The Processing Unit

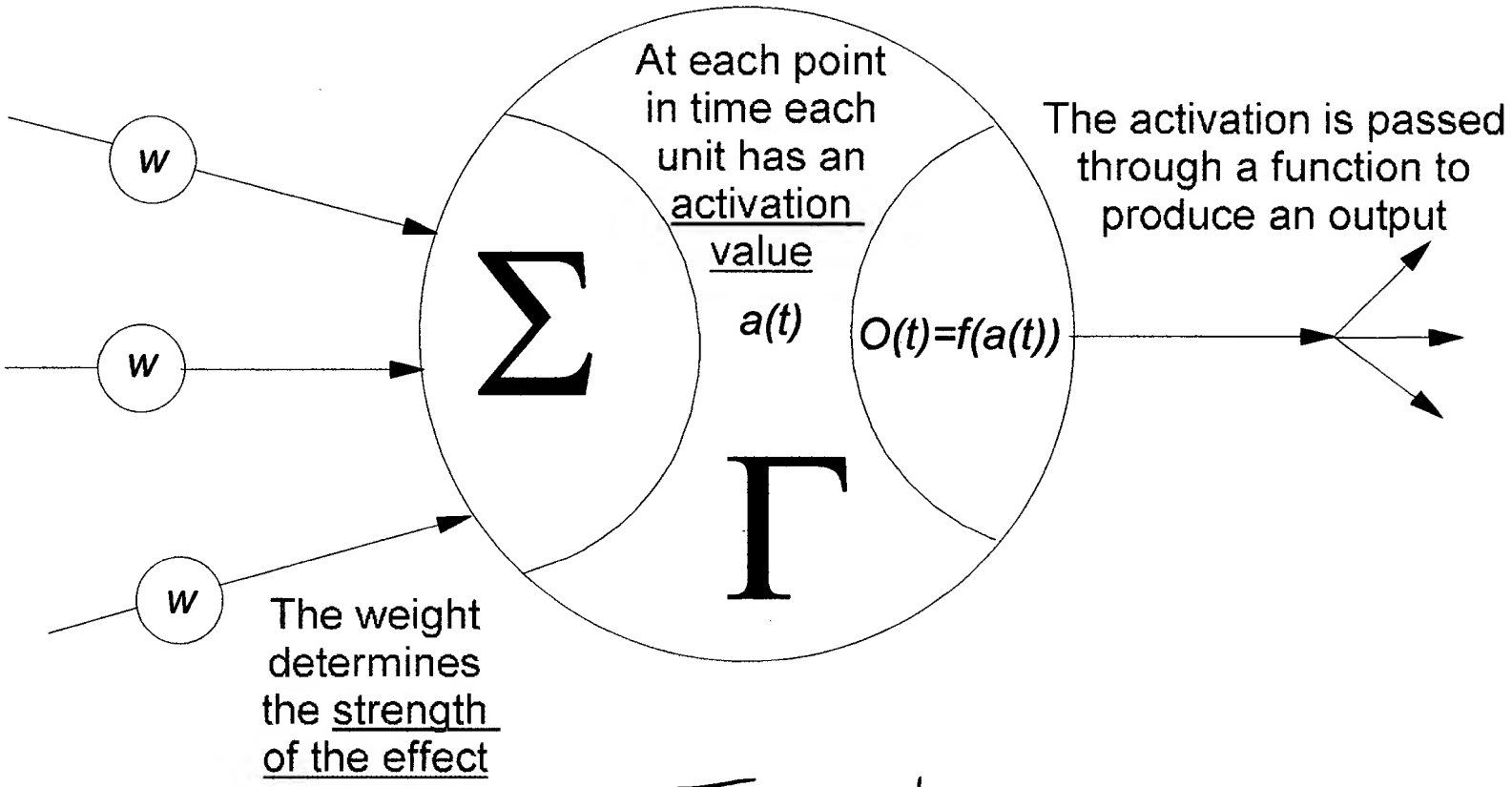


Figure 1c

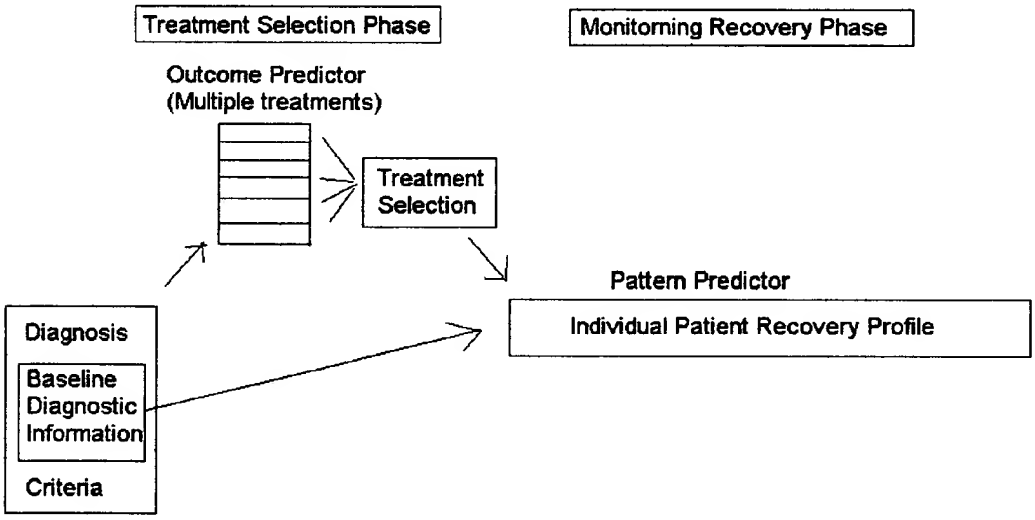
Depression Disorder Integrated Model (DDIM)

A method of choosing treatment based on selection (after outcome predictions are made) and then a method for generating a profile for patient monitoring patient response to specific treatment based on a method for prediction treatment specific response patterns.

Diagnosis and other baseline data are collected and transmitted as input to the "Outcome Predictor." The outcome predictor has been trained on other (prior) patients baseline and outcome data. Predictions and confidence limits are generated for a number of treatment options.

Treatment selection suggestion is made by the system for evaluation and consideration by a clinician, who has the final responsibility for the treatment selection.

The baseline data and the chosen treatment are input to the Pattern Predictor



Joanne

Figure 2

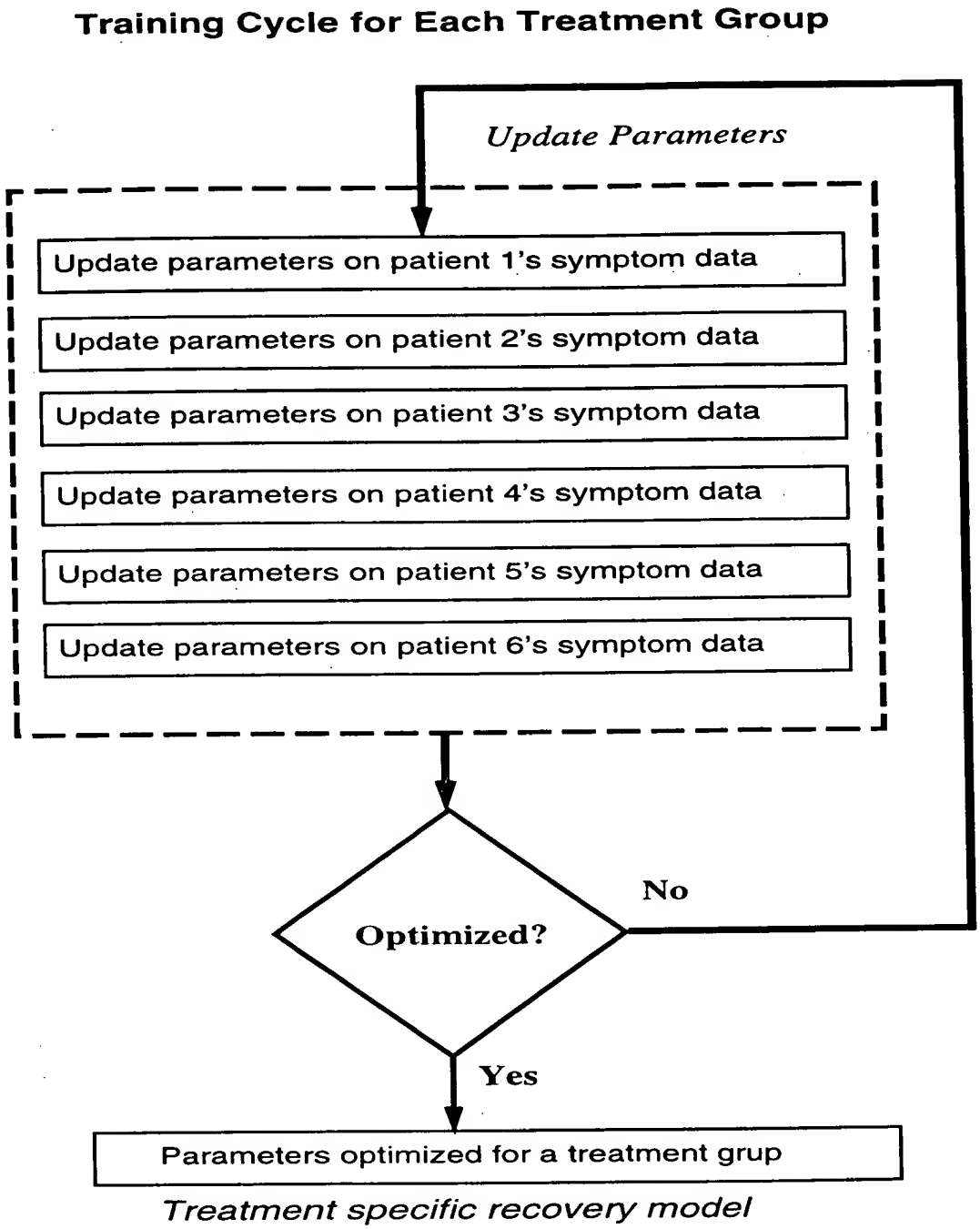


Figure 3·2: Training cycle for each treatment group. Each of the two models with separate sets of parameters, but with a same architecture, was trained by cycling through individual data within the respective treatment group. After each cycle, the cost function (which reflects the degree of fit of the model predictions to the actual data) was evaluated to determine the completion of training.

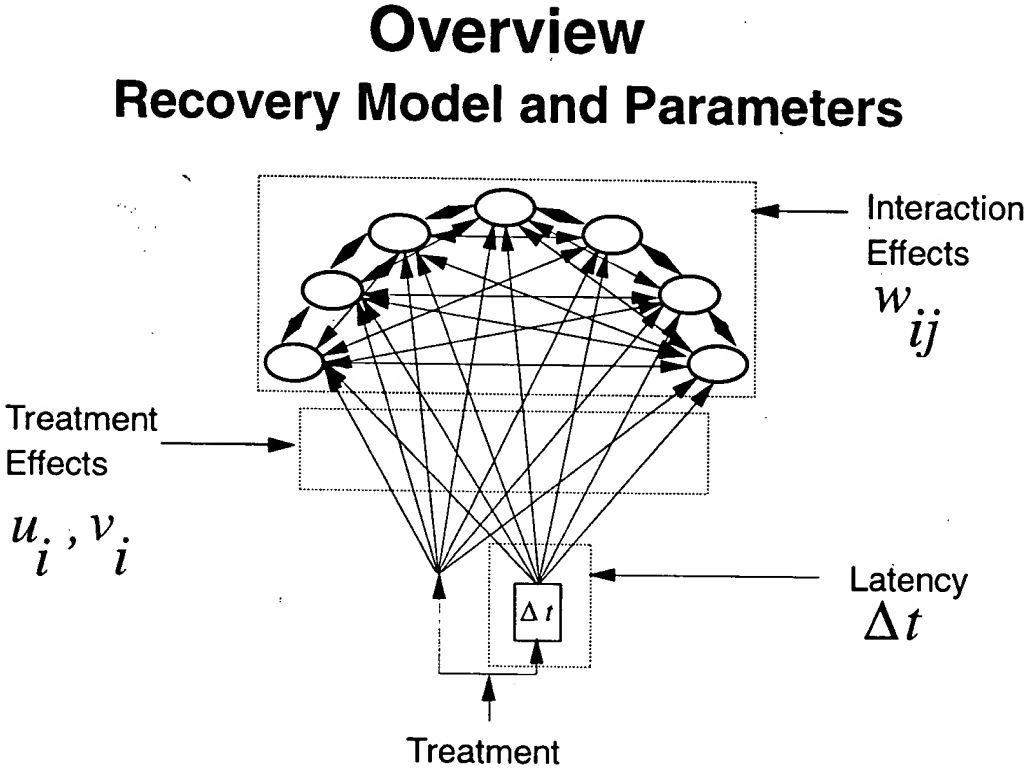


Figure 3-3: Overview of the recovery model. Ellipses represent symptom factors, arrows between the symptom factors indicate each symptom factor can influence every other symptom factor.

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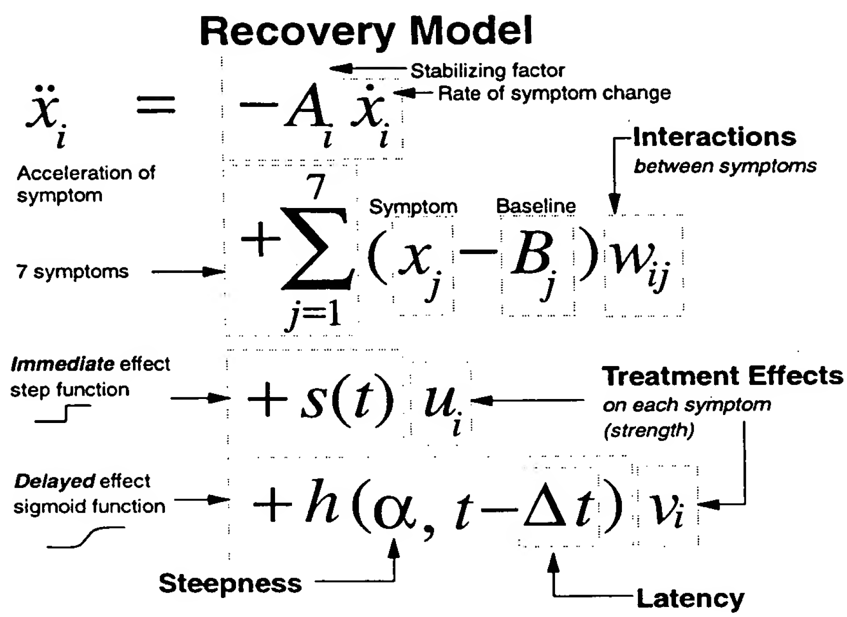

$$\ddot{x}_i = -A_i \dot{x}_i + \sum_{j=1}^{7} (x_j - B_j) w_{ij} + s(t)\, u_i + h(\alpha, t - \Delta t)\, v_i$$

Figure 3·4: The annotated second order differential equation used to model the pattern of recovery.

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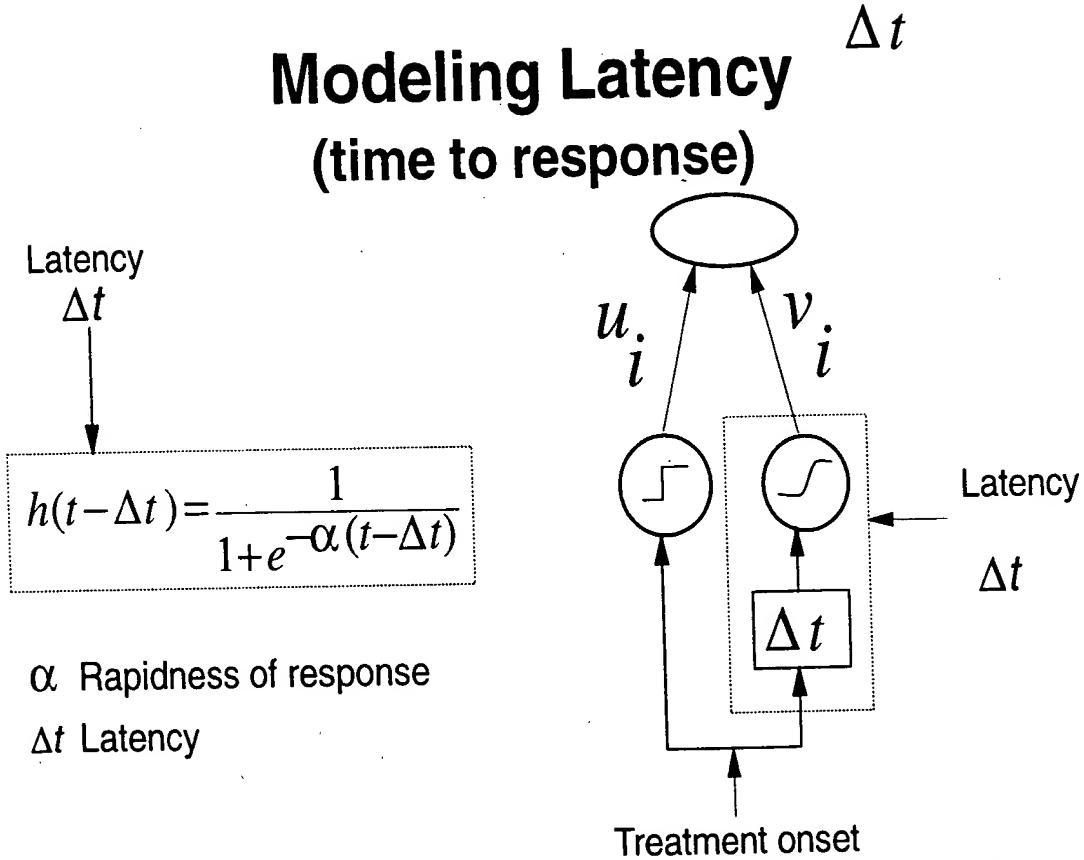

Figure 3·5: Direct effects of treatment are either immediate (step function) or delayed (sigmoid function). Delays are estimated by treatment from the patient data, using an optimization procedure.

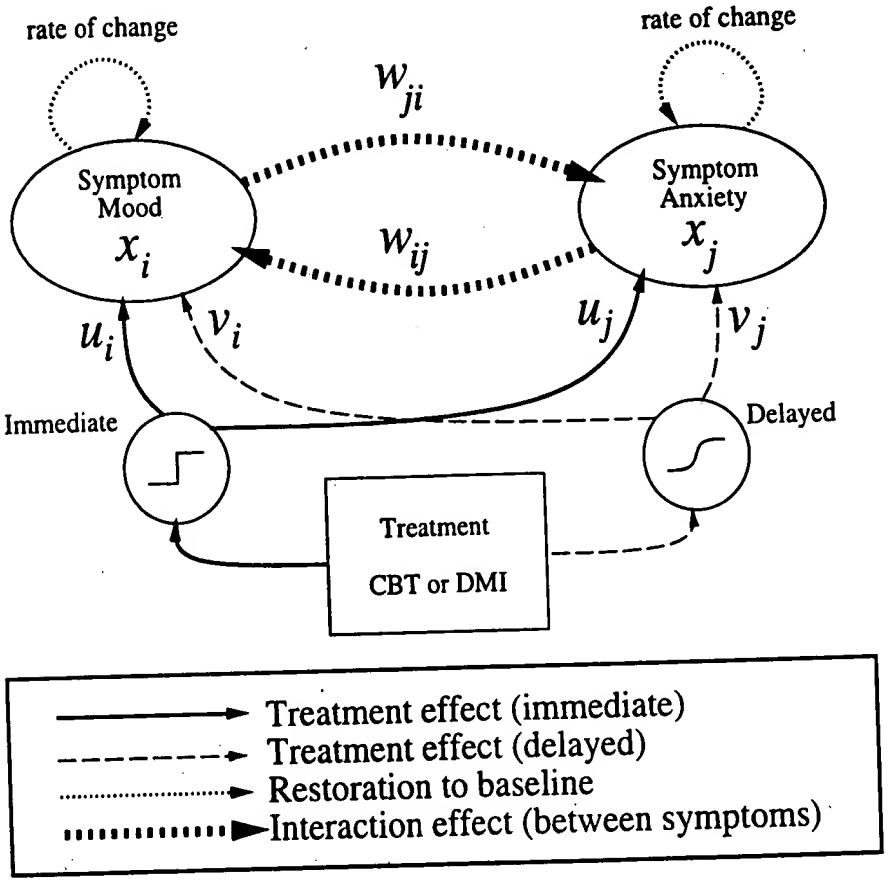

Figure 3·6: Direct effects and interactions in the recovery model. u_i represents the strength of the immediate effect of treatment on symptom node i; v_i represents the strength of the delayed effect of treatment on symptom i; and w_{ji} and w_{ij} represent the interaction between the symptoms: the strength of the effect of symptom i on symptom$j$ and the strength of the effect of symptom j on symptom$i$, respectively.

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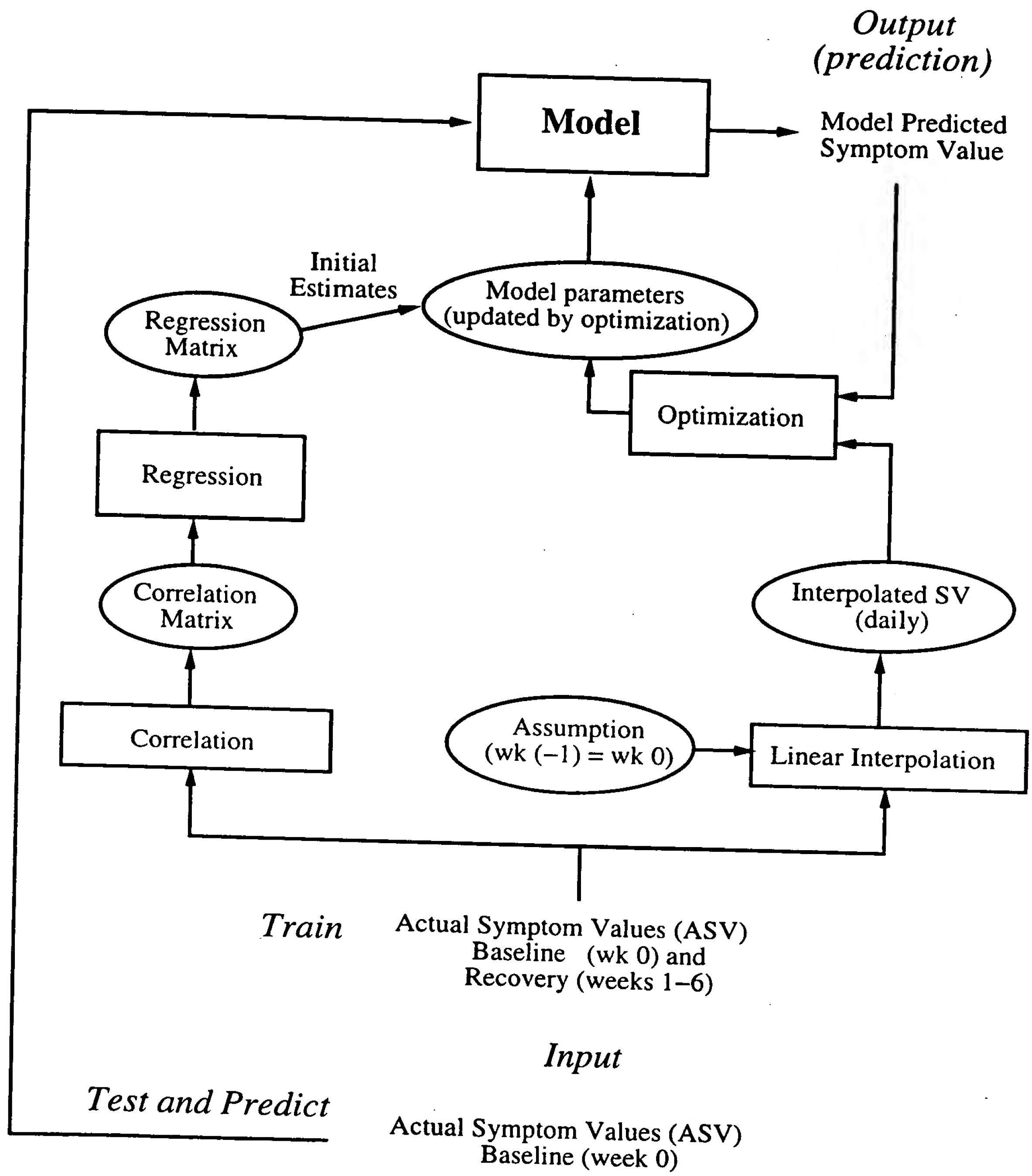

Figure 3·7: Overview of Training Process. Parameters were initialized with regression matrix which was calculated from actual symptom values (ASV) by correlation and regression analyses. The model used these initial parameters to predict symptom values (model symptom values, MSV) of each patient from baseline. The optimization process iteratively modified parameters to minimize the discrepancy between MSV and ASV.

Training the Model

estimated

$$L=\int_0^T \sum_{ik}\left(\left(X_{ik}-\hat{X}_{ik}\right)^2+\mu_{ik}\left(\dot{\hat{X}}_{ik}-f\left(\hat{X}_{ik}\right)\right)\right)dt+K\sum_j P_j^2$$

actual

L = Error term
k = patients
i = symptoms
j = parameter
X = data

Obtain optimized parameters
- -fit patient data
- -train on entire recovery period
- -minimize error term L
- -gradient descent on parameters

Figure 3-8: A schematic description of the cost function L. The formula inside the integration has two terms. By minimizing the first term, discrepancies between estimated and actual patterns of recovery are minimized. The second term is a constraint term which states that the differential equation must hold.

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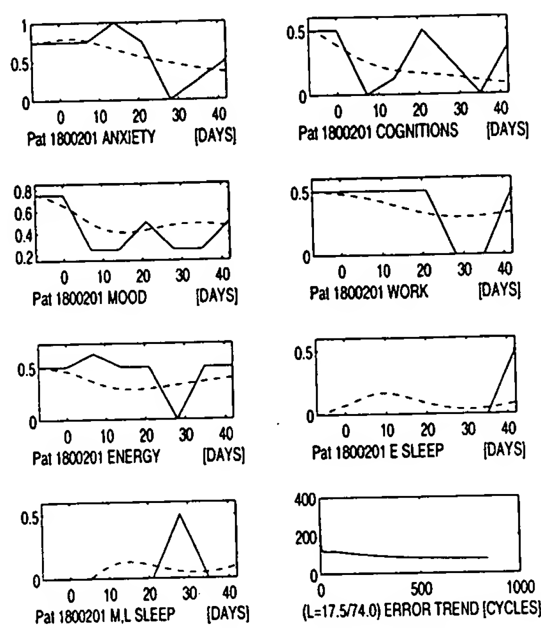
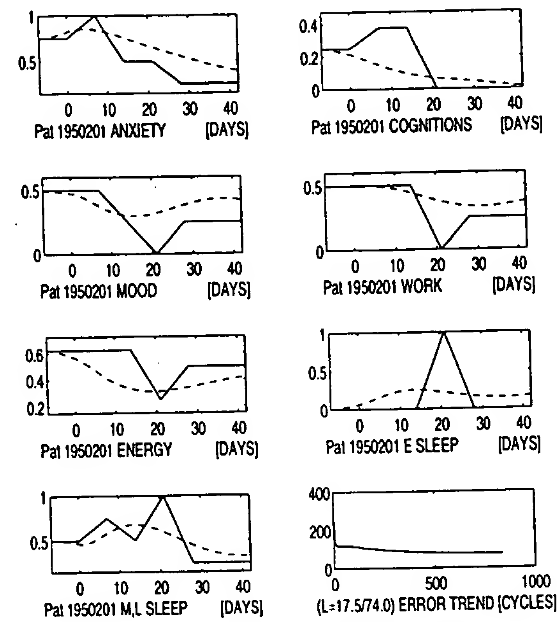
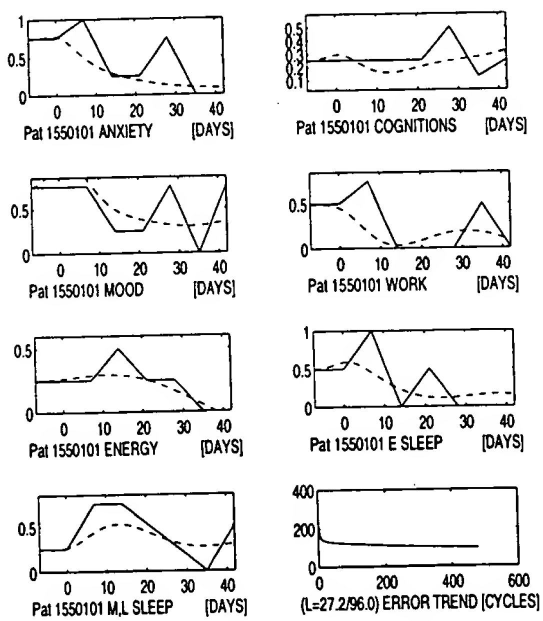


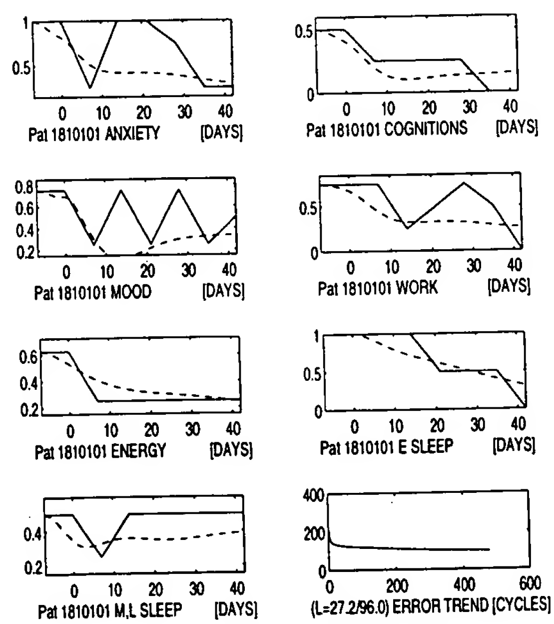
(a) CBT patient 180



(b) CBT patient 195

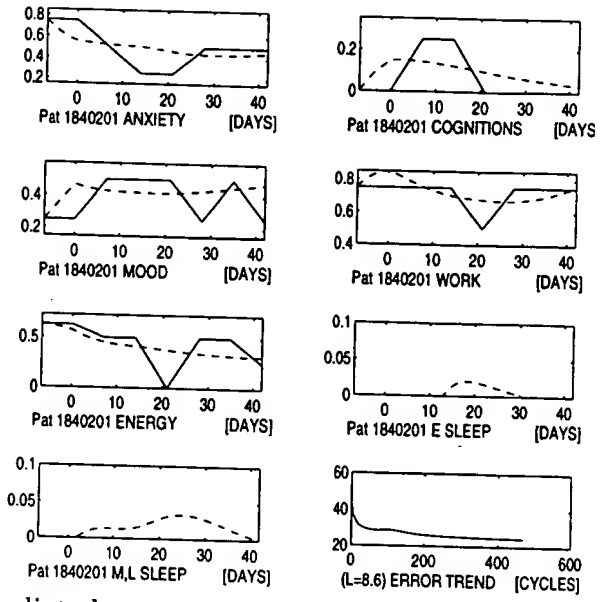


(c) DMI patient 155

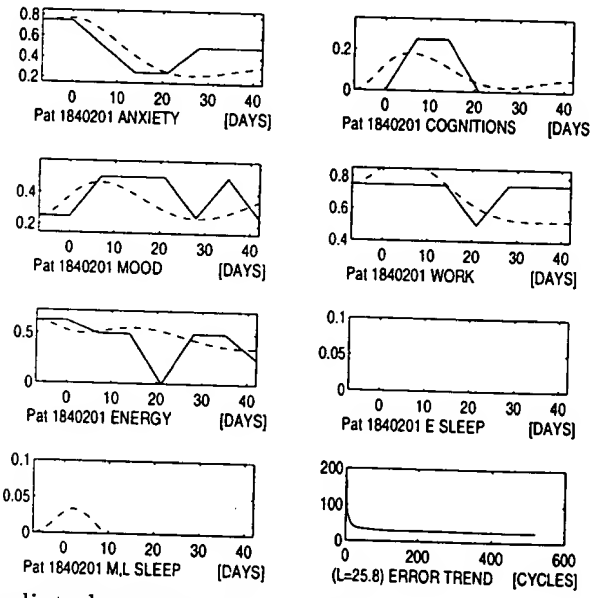


(d) DMI patient 181

Figure 3·10: Individual patterns of recovery. Plots, except the one at the bottom right, show patterns of recovery. Solid lines show actual patterns, dotted lines show predicted patterns. Numbers shown at vertical axis are scaled such that the possible maximum symptom factor value yields 1.0. The plot at the bottom right shows the error (L) on the ordinate axis plotted against number of training cycles on the abscissa.

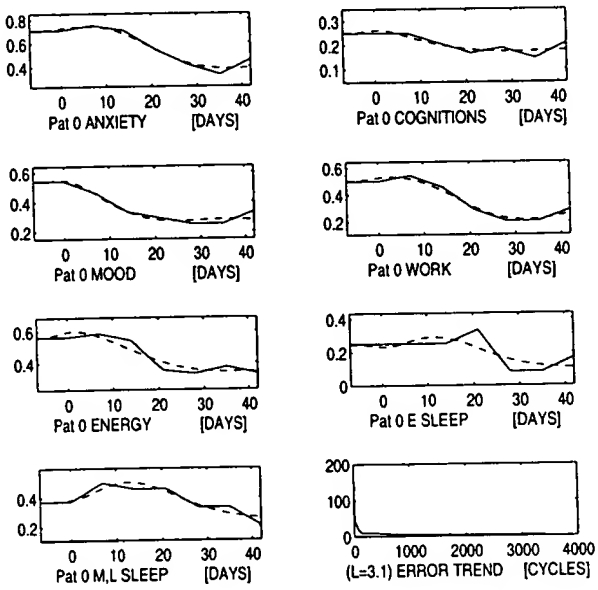


(a) Predicted patterns of recovery by shunting equations

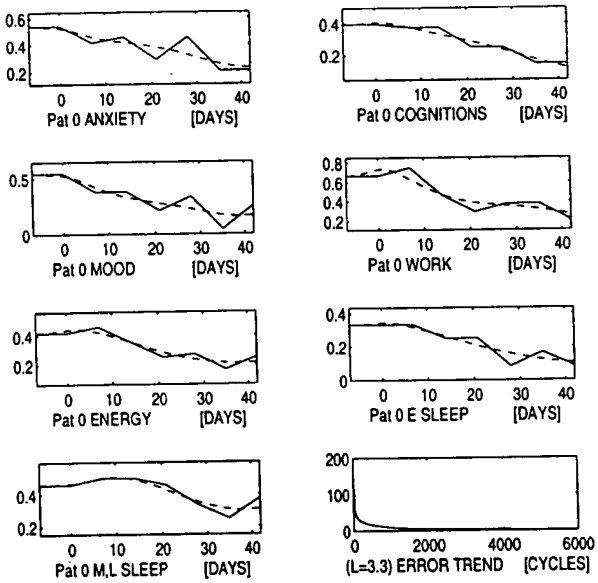


(b) Predicted patterns of recovery by second order equations

Figure 3-9: Predicted patterns of recovery by (a) shunting and (b) second order equations. In both (a) and (b), plots except the sub-plot at the bottom right, show patterns of recovery. Solid lines show actual patterns, dotted lines show predicted patterns. Numbers shown at vertical axis are scaled such that the possible maximum symptom factor value yields 1.0. The plot at the bottom right in both (a) and (b) shows the error (L) on the ordinate axis plotted against number of training cycles on the abscissa. Note that the absolute values of the error measure L cannot be compared between shunting and second order equations, because the latter includes errors in the derivatives of L.



(a) Predicted and actual mean patterns of recovery (CBT)



(b) Predicted and actual mean patterns of recovery (DMI)

Figure 3·11: Predicted and actual recovery patterns of patient data mean. (a) mean of six CBT responders (b) mean of six DMI responders. In both (a) and (b), all plots except the subplots at the bottom right, show mean patterns of recovery. Solid lines show actual mean patterns, dotted lines show predicted mean patterns. Numbers shown at vertical axis are scaled such that the maximum possible symptom factor value yields 1.0. The plot at the bottom right in both (a) and (b) shows the error L plotted on the ordinate axis against number of training cycles on the abscissa. Pat 0 indicates the patient averaged patient data were used.

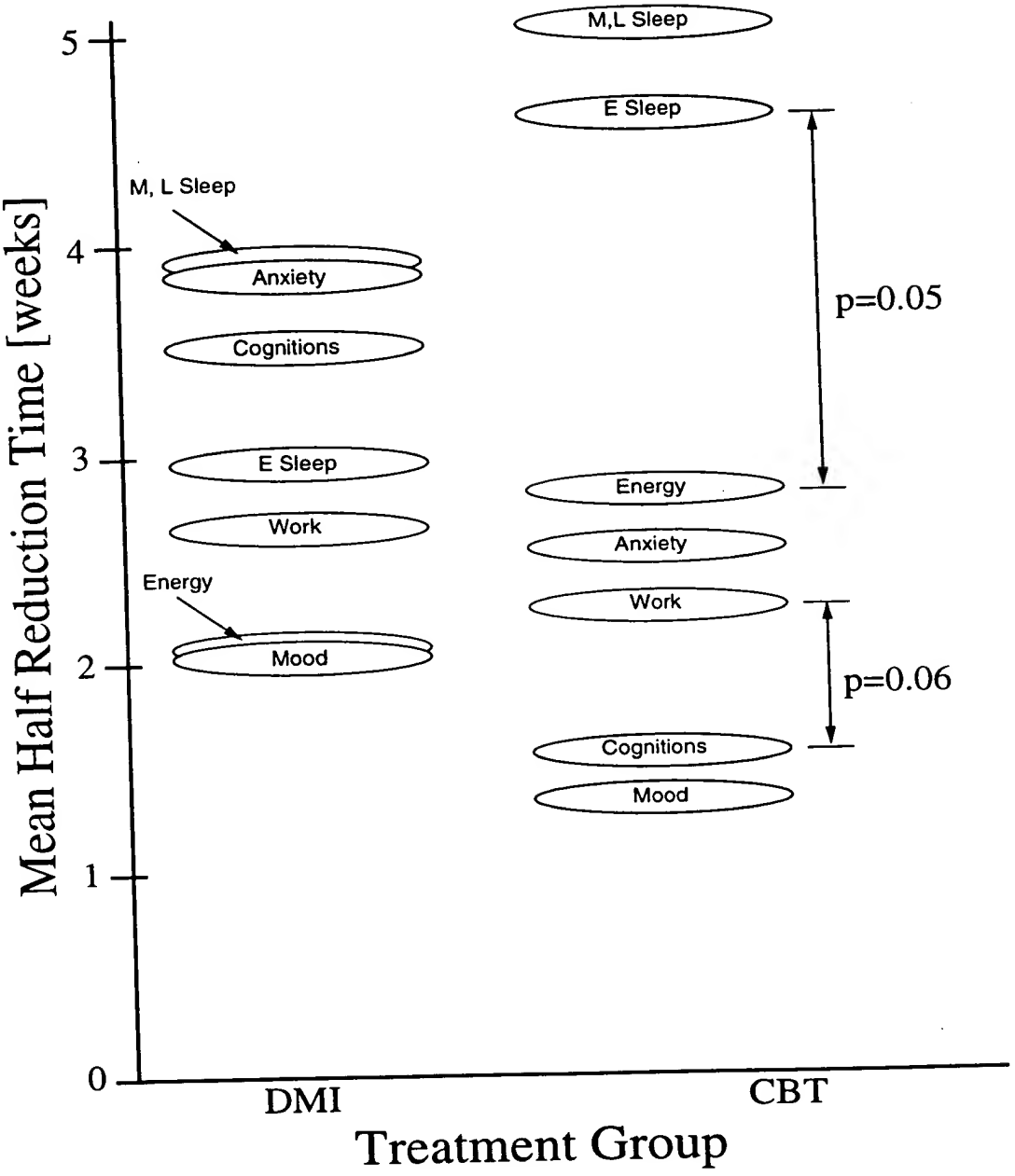
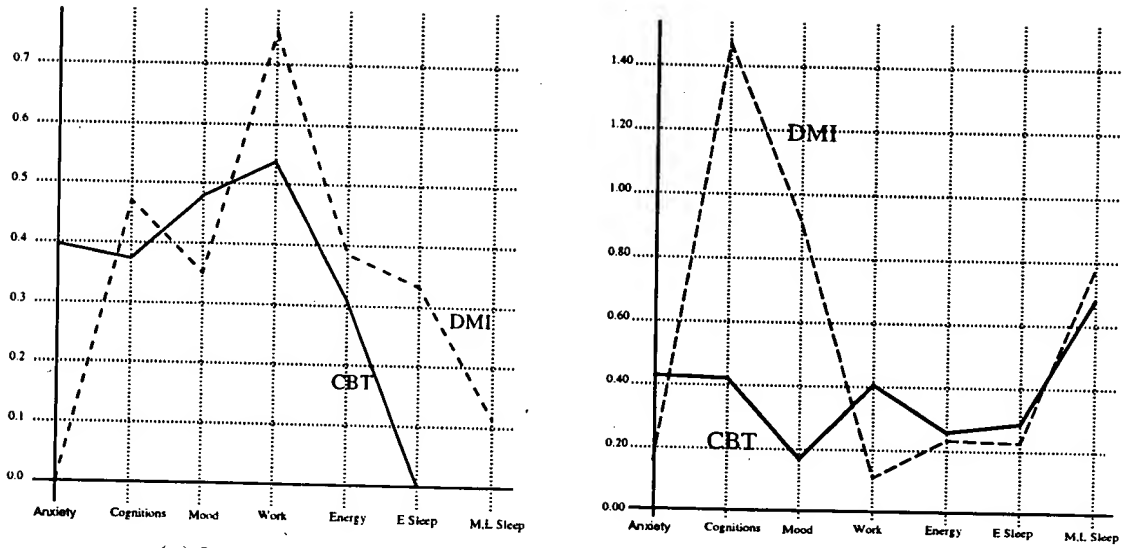


Figure 3·13: Predicted CBT and DMI temporal response sequence of symptom improvement. The vertical axis shows the mean half reduction time in weeks; the horizontal axis has no meaning. Symptom names are placed vertically at their mean half reduction time. Significant difference ($p < 0.05$ after rounding) between half reduction times of energy and early sleep disturbance. There is a trend ($p < 0.10$ after rounding) for a split between cognitions and work in CBT responders. In DMI there were no significant differences (or trends) in the sequence.



(a) Immediate Treatment Effects

(b) Delayed Treatment Effects

Figure 3-14: Comparison of model's predicted immediate (left) and (b) delayed (latent) direct effects of treatment on symptoms for Cognitive Behavioral Therapy and Desipramine. A solid line represents CBT coefficient values, a dashed line represents DMI coefficient values. Symptom are represented along the x-axis. The coefficient values the parameter optimization procedure indicate the strength of the effect on the symptom at the time the effect takes place, and are placed on the y-axis. For example, the delayed effect of cognitions for desipramine occurs at 3.4 weeks with a magnitude of almost 1.5, whereas the delayed effect of cognitions of CBT takes place at 1.2 weeks and has a magnitude of about 4.2. A zero indicates that the model predicted the symptom would worsen initially.

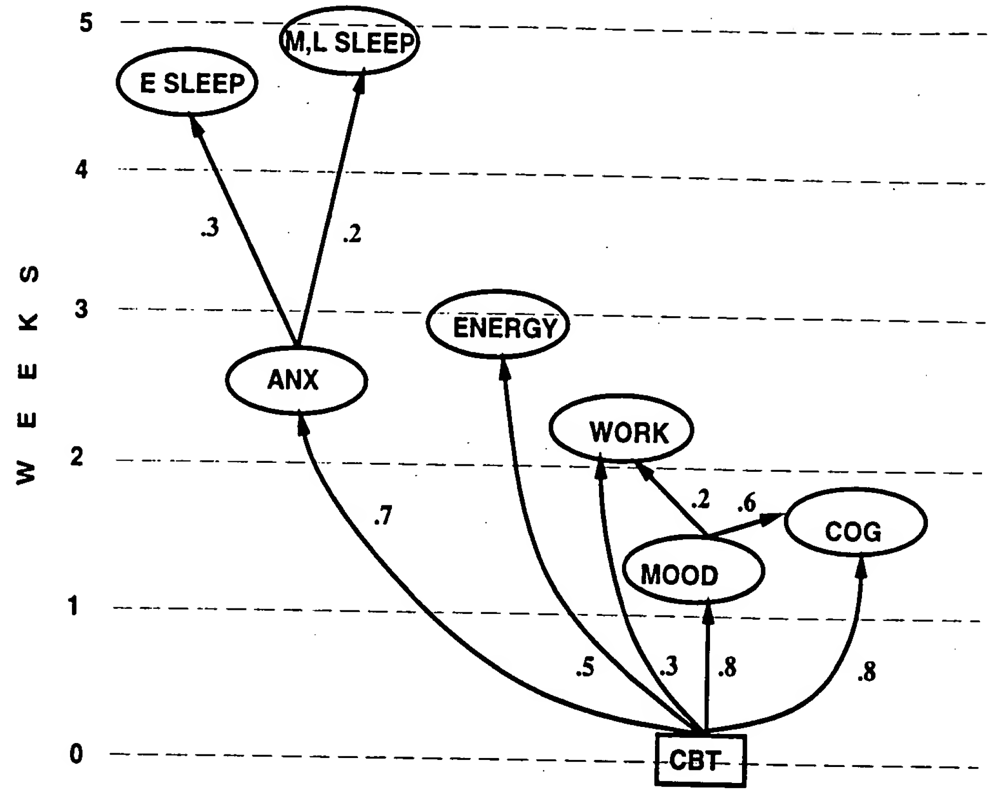


Figure 3·15: Graphic representation of the sequence of symptom factors in recovery with Cognitive Behavioral Therapy treatment for the second order system. Vertical positions of the symptoms represent half-way-reduction time, arrows represent strong impacts and interactions, and corresponding numbers indicate the strength of the impact or interaction. See text for formula.

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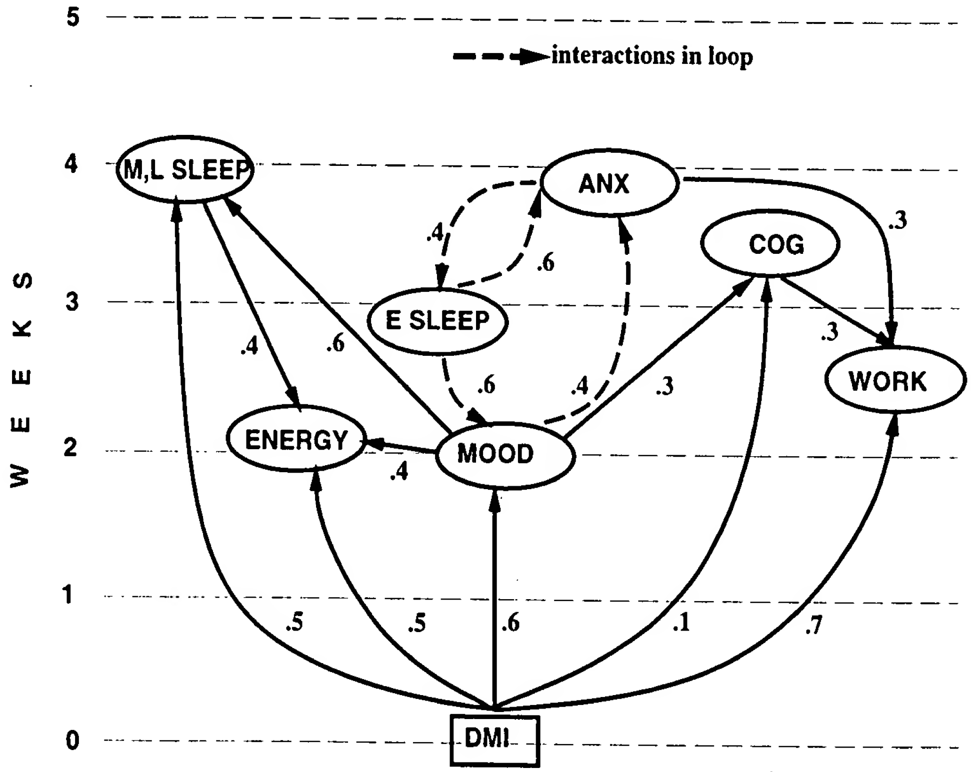

Figure 3-16: Graphic representation of the sequence of symptom factors in recovery with Desipramine treatment for the second order model. Vertical positions of the symptoms represent half-way-reduction time, arrows represent strong impacts and interactions, and corresponding numbers indicate the strength of the impact or interaction. Dotted arrows show the interactions that operate in loops. See text for formula.

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Prediction of Outcome from Baseline Symptoms

Symptom	Treatment													
HDRS Item	Other	Tricyclic							MAOI		SSRI	Psycho-therapy		ECT
		Ami	Nor	IMI	DMI	Clo	Lev	Map	Phe	Tran	Flu	IPT	CBT	ECT
Severity	5,9–	10–		10–,11,16+,17+	1,8	8,13	3–	3–,6+	17+		1	16+	7	14–
Depressed Mood	2	10–,15	4	10–,11	1,8	8			4	18+	1			14–
Feelings of Guilt		15		11	1,8	8				18	1			14
Suicide	5	15		11	1,8	8				18	1			14
Insomnia: early	2	15	4	11	1,8	8			12,4	18	1			14
Insomnia: middle	2	15–	4	11	1,8	8			12,4	18–	1			14
Insomnia: late	2	15	4	11,12+	1,8	8			4	18–	1			14
Work and interests		15	4	11,12	1,8	8			11	18	1			14–
Retardation	2	10,15	4	10,11,12+	1,8	8			4	18+	1			18
Agitation	2	10,15		10,11,12	1,8	8			12,4	18	1			14–
Anxiety: somatic	2	10,15	4	10,11	1,8	8			4	18	1			
Anxiety: psychic	2	10,15	4	10,11	1,8	8			4	18	1			
Somatic: gastrointestinal		15–		11	1,8	8				18	1			14–
Somatic: general		10,15	4	10,11	1,8	8			4	18	1			
Genital symptoms		15		11,12	1,8	8			11	18	1			14
Hypochondriasis		15–	4	11	1,8	8			4	18	1			14
Loss of weight [or change]	2	15	4	11,12	1,8	8			12,4	18+	1			14
Insight		15+		11	1,8	8				18	1			
Diurnal variation		15	4	11,12	1,8	8			12,16	18	1			14
Depersonalization and derealization		15		11	1,8	8				18	1			
Paranoid symptoms	2	15		11	1,8	8				18	1			
Obsessive and compulsive	2	15		11	1,8	8				18	1			

Table 4.1: Prior attempts to predict outcome from Hamilton Depression Rating Scale scores (symptoms) and severity (total HDRS) of depressive symptoms. Independent variables are the HDRS items described under the column *Symptom*. Numbers are indices into Table 4.2 where the citations are listed and indicate that the symptom at baseline was not found to be a significant predictor of outcome. Underlined numbers are also indices into Table 4.2, but indicate the symptom at baseline was found to predict outcome. Blank entries indicate that the significance of the symptom to predict outcome was not reported. (+) indicates greater intensity predicted better response; (–) indicates greater intensity predicted poorer response. See Table 4.2 for key to citation references. Other=S-adenosyl methionine (Carney et al., 1986), ECT or unspecified antidepressant medication (Hinrichsen & Hernandez, 1993), unspecified antidepressant medication (Katon et al., 1994); Tricyclic=tricyclic antidepressant medications; MAOI=monoamine oxidase inhibitor antidepressant medications; SSRI=selective serotonin reuptake inhibitors; ECT=electroconvulsive therapy; Ami=amitriptyline; Nor=nortriptyline; IMI=imipramine; DMI=desipramine; Clo=clomipramine; Lev=levoprotiline; Map=maprotiline; Phe=phenelzine; Tran=tranylcypromine; Flu=fluoxetine; IPT=interpersonal therapy; CBT=cognitive behavioral therapy.

1. Bowden, C., Schatzberg, A., Rosenbaum, A., Contreras, S., Samson, J., & Dessain, E. (1993). Fluoxetine and desipramine in major depressive disorder. *Journal of Clinical Psychopharmacology*, **13**, 305–311.
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18. White, K. & White, J. (1986). Tranylcypromine: Patterns and predictors of response. *Journal of Clinical Psychiatry*, **47**, 380–382.

Table 4.2: Reference index for Table 4.1, prior research in prediction of outcome from baseline clinical symptoms.

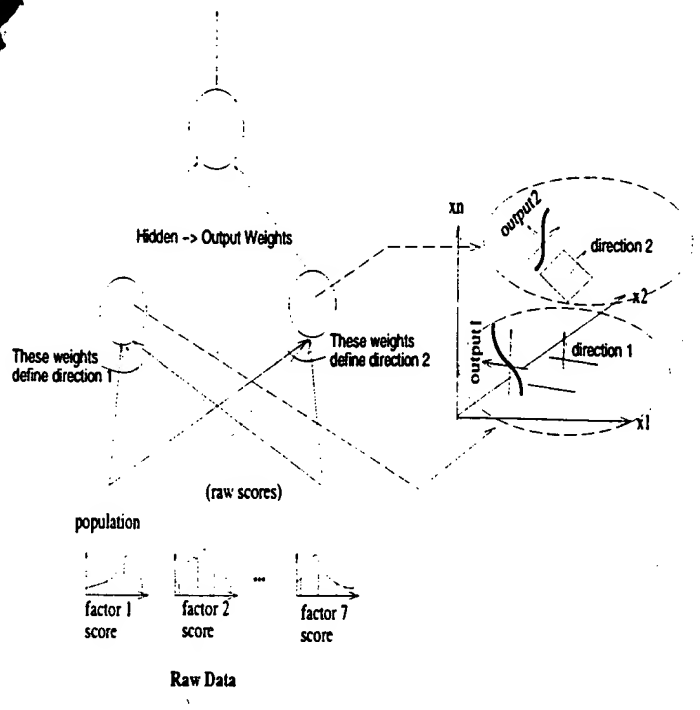

Figure 4·1: Nonlinear mapping of backpropagation. Each hidden node finds a direction in the input space (illustrated by an arrow perpendicular to a small square piece) to which the output is sensitive to. The output of each hidden node goes through a nonlinear output function before being weighted and summed at the output node.

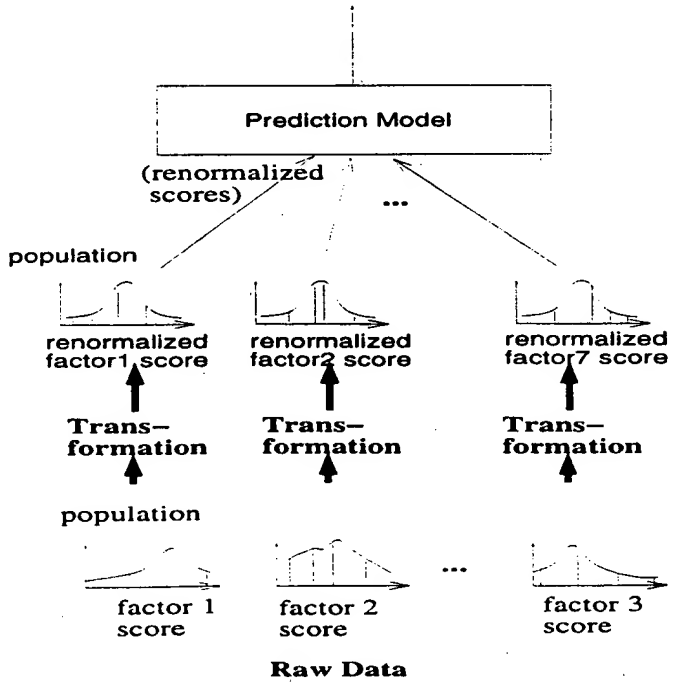

Figure 4·2: Schematic representation of the effect of normalizing transformations on reducing nonlinearity of score-to-output relationships (or skewedness of distributions). In the transformation, the area under the curve is preserved. The transformation redistributes the position of the data values along the x-axis in order to preserve the areas under the curve between adjacent scores values while redistributing these data to best approximate a normal distribution. Equal areas under the curve between percentiles map to equal areas under the curve in the new distribution.